2019 Multiscale Modeling Consortium Meeting - Translation and Dissemination (March 6-7, 2019)

Poster *Abstract Submission Form*

PI(s) of MSM U01: Mark Alber, John Weisel
Institution(s): UC Riverside/University of Pennsylvania
MSM U01 Grant Number: U01HL116330
Title of Grant: Multiscale modeling and empirical study of a mechanism limiting blood clot growth

Abstract Authors

Oleg Kim[1,2], Rustem Litvinov[1], Mark Alber[2], John Weisel[1]

[1]University of Pennsylvania Perelman School of Medicine, Department of Cell and Developmental Biology, Philadelphia, Pennsylvania 19104, USA
[2]University of California Riverside, Department of Mathematics, Riverside, California 92505, USA

Abstract Text

Under (patho)physiological conditions, activated platelets change their morphology, express adhesive molecules, undergo aggregation, secrete procoagulant substances, and induce mechanical contraction (retraction) of blood clots. We tested the hypothesis that activated platelets undergo late alterations that determine their fate and may have a pathogenic importance in thrombotic and hemostatic disorders. We used a combination of confocal microscopy, immunofluorescence, biochemical and biomechanical measurements to study deferred structural, metabolic, and functional consequences of thrombin-induced activation of viable human platelets, either suspended in platelet-rich plasma or isolated by gel-filtration. Platelets in thrombin-induced plasma clots initially underwent shape changes characteristic of platelet activation, but in about 30 min many platelets and platelet aggregates broke up into organelle-containing vesicular fragments. Concurrently with the fragmentation, thrombin-activated platelets displayed dramatically altered intracellular distribution and concentration of F-actin. Synchronously with the structural alterations, thrombin induced a time-dependent reduction of the mitochondrial membrane potential and metabolic ATP depletion in platelets that strongly and inversely correlated with an increase of reactive oxygen species and fraction of disintegrated platelets. Unexpectedly, no activation of caspase 3/7 was detected in platelets after 90 min of treatment with thrombin. Meanwhile, fluorescence of calpain cleavage products detected in platelets 90 min after thrombin treatment was 6.5-fold higher compared to untreated platelets. Moreover, calpain inhibition caused a ~30-min delay in the commencement of thrombin-induced platelet fragmentation. To conclude, thrombin-activated platelets undergo time-dependent dysfunction and structural disintegration into subcellular particles. The lack of caspase activity and increased calpain activity in energetically exhausted platelets undergoing fragmentation suggests a calpain-dependent platelet death pathway that is an underappreciated mechanism for enhanced elimination of platelets from the circulation in (pro)thrombotic conditions or under other conditions once they have performed their functions.